

**UNITED STATES DEPARTMENT OF COMMERCE****Patent and Trademark Office**Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DK

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
-----------------	-------------	----------------------	---------------------

09/544, 776 04/07/00 WEI

D 1561.003/200

HM12/0226

EXAMINER

CHIRON CORPORATION
INTELLECTUAL PROPERTY R338
PO BOX 8097
EMERYVILLE CA 94662-8097

ZARA, J

ART UNIT	PAPER NUMBER
----------	--------------

1635

8

DATE MAILED:

02/26/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	09/544,776	WEI ET AL.
	Examiner	Art Unit
	Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on _____.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-29 is/are pending in the application.
 - 4a) Of the above claim(s) 11-22, 26 and 27 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-10, 23-25, 28 and 29 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) Notice of References Cited (PTO-892)
- 16) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4.
- 18) Interview Summary (PTO-413) Paper No(s). _____
- 19) Notice of Informal Patent Application (PTO-152)
- 20) Other: _____

File

DETAILED ACTION

Claims 1-29 are pending in the instant application.

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-10, 23-25, 28 and 29, drawn to compositions and methods comprising nucleic acids, classified in class 436, subclass 6.
- II. Claims 11-16 and 20-22, drawn to polypeptides, classified in class 530, subclasses 300 and 350.
- III. Claims 17-19, drawn to antibodies, classified in class 530, subclass 387.1.
- IV. Claims 26 and 27, drawn to methods of decreasing activity of a protein comprising phosphorylation, classified in class 530, subclass 352.

The inventions are distinct, each from the other because of the following reasons:

The nucleic acids of Group I, the polypeptides of Group II, and the antibodies of Group III are chemically, biologically, structurally and functionally distinct from each other and thus one does not render the other obvious. The polypeptides and antibodies of Group II and III respectively are not required to produce each other, nor are they required to produce the nucleic acids of Group I, and the nucleic acids of Group I are not required to produce the polypeptides and antibodies of Groups II and III (which can be produced synthetically or isolated from cells). Therefore, the inventions of the these different and distinct groups are capable of supporting separate patents.

Art Unit: 1635

The products of Groups I-III are biologically and functionally different and distinct from the methods of Group IV and thus one does not render the other obvious. The nucleic acids, polypeptides and antibodies of Groups I and II and III are not used in the methods of Group IV. The operation, function and effects of the products of Groups I and II and III are completely different and distinct from the operation, function and effects of the methods of Group IV, which comprise post-translational modifications and activation of other, distinct proteins. Therefore, the inventions of these different, distinct groups are capable of supporting separate patents.

The methods of Group I and IV are biologically and functionally different and distinct from each other and thus one does not render the other obvious. The methods of Group I comprise steps which are not required for or present in the methods of Group IV: inhibition of expression (Group I) and post-translational modification of translated proteins (Group IV). Therefore, the inventions of these different, distinct groups are capable of supporting separate patents.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Jane Potter on or about January 24, 2001, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-10, 23-25, 28 and 29. Affirmation of this election must be made by applicant in replying to this

Art Unit: 1635

Office action. Claims 11-22, 26 and 27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1(c) recites the limitation "said amino acids about 197 and about 236 are joined by a peptide bond" in lines 8-9 of claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear what SEQ ID No. the amino acids "about 197-236" of 1(c), "288-366" of 1(d) and both "197 and about 236" as well as "288 and about 336" of 1(e) are referring to.

Art Unit: 1635

Claims 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 reads on a method of inhibiting cell growth comprising transfecting said cell with a polynucleotide which is the complement of a mRNA molecule encoding SEQ ID NO: 2, which sequence comprises an polypeptide comprising 373 amino acids. The length of the complement nucleotide sequence comprises 1122 nucleotides. The length of this molecule cannot be both 1122 nucleotides and between 8 and 50 nucleotides.

Claims 1 and 5-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the revised guidelines for written description, effective December, 1999. The specification does not describe or disclose the elements which are essential to various functions of the claimed invention, which elements include those which are essential to defining the length of the nucleic acid and amino acid molecules, as well as defining the number of modifications within these molecules, and which elements include the nature and number of conservative amino acid substitutions of SEQ ID NO: 2. The specification does not disclose or describe the elements which are essential to the genus comprising all permissible conservative amino acid substitutions of SEQ ID NO: 2, or parts thereof, or what comprises at

Art Unit: 1635

least 80% identity of those molecules described in claims 1(a) through 1(j). Furthermore, the specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the genus comprising the lengths, modifications, and substitutions of the molecules of the claimed invention, nor what attributes are concisely shared by conservative amino acid substitutions of SEQ ID NO: 2, or the parts thereof. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between members of the genus is permitted. Concise structural features that could distinguish structures within the genus from others are missing from the disclosure. No common structural attributes identify the members of the genus comprising all those molecules described in the claims, nor are the permissible conservative amino acid substitutions of SEQ ID NO: 2 defined. The general knowledge and level of skill in the art do not supplement the omitted description because *specific*, not general, *guidance* is what is needed. The specification fails to teach or adequately describe a representative number of species in the genus such that the common attributes or characteristics concisely identifying members of the proposed genus are exemplified. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed. Thus, Applicant was not in possession of the claimed genus.

Claims 23-25, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting cell growth in vitro comprising the administration of antisense or ribozymes targeting Nogo B, does not reasonably provide

Art Unit: 1635

enablement for methods of inhibiting cell growth *in vivo* comprising the administration of antisense targeting Nogo B. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of cell growth inhibition *in vitro* and *in vivo*, and methods of inhibiting Nogo B activity *in vitro* and *in vivo*, comprising the administration of antisense or ribozymes targeting Nogo B.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed. This determination is based on several factors which, when considered together, illustrate that the art of gene delivery, expression and/or inhibition is in its infancy and highly unpredictable. The discussion is also based on references whose teachings show that, despite a tremendous amount of experimentation by highly skilled artisans in the field of gene delivery and expression *in vivo*, there remain significant hurdles known in the art to make and/or use the invention over the scope claimed.

The nature of the invention. Methods of targeting nucleic acids into host cell *in vivo* fall into the broad area known as gene therapy methods. While delivery of nucleic acids in and of itself is not considered as therapy per se, *in vivo* delivery shares many of the obstacles recognized for the actual therapy methods because successful therapy methods are for the most part based on the ability to deliver exogenous nucleic acids to cells or tissues of interest.

Art Unit: 1635

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene delivery. Crystal points out that some disadvantages of using gene transfer vectors include their general inefficiency at achieving successful gene transfer and a general lack of available data regarding repetitive administration of DNA to whole organisms (page 405, second paragraph). Schofield *et al* also teach advantages delivery of genes *in vivo*, although many of the details regarding cell targeting, cell entry and gene expression in target cells remain highly speculative. Schofield *et al* caution that there are significant variations that exist between animals, and state that only limited conclusions could be drawn from animal studies which may be applied to the treatment of humans (pages 61-64). Verma *et al* teach the problems of gene delivery in whole organisms using various approaches, including liposomes as delivery agents, and state that such approaches suffer from limitations relating to poor efficiency of delivery and the transient expression of delivered genes (page 239, second paragraph from the end). Friedmann teaches that gene transfer by liposomes is much less efficient than virus-mediated transfer (page 100, last paragraph-page 101, first paragraph), while, according to Friedmann, the gene therapy field as a whole currently lacks convincing therapeutic benefit (page 96). Palu *et al* teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2. Branch and Crooke teach that the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and

Art Unit: 1635

delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke).

While these references acknowledge the usefulness of gene therapy including lipid mediated delivery and the possibility of developing efficacious strategies in the future, they also illustrate that there are numerous obstacles to successful gene therapy which current methods still must overcome. As such, the disclosed utilities of the present specification which are drawn to gene delivery methods are credible. The present rejection, therefore is not for lack of utility, but rather for lack of enablement for the methods claimed.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting Nogo B activity *in vivo*, nor of inhibiting cell growth *in vivo* comprising the administration of antisense or ribozymes targeting Nogo B.

The specification teaches the *in vitro* inhibition of cell growth and inhibition of Nogo B activity in target cells *in vitro*, which cells harbor nucleic acids encoding Nogo B. The specification fails to teach the successful delivery of antisense or ribozymes and subsequent inhibition of the appropriate target gene in a whole organism. One skilled in the art would not accept on its face the examples given in the specification of *in vitro* inhibition as being correlative or representative of the administration of antisense or ribozymes in any and/or all organisms such that the target gene Nogo B is appropriately inhibited and further where target

Art Unit: 1635

cell growth is inhibited in view of the lack of guidance in the specification and known unpredictability associated with the administration and *in vivo* delivery of antisense or ribozymes. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with *in vivo* delivery and treatment effects (i.e. cell growth inhibition) provided by antisense or ribozymes administered, and specifically regarding the instant target gene Nogo B.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods for the inhibition of Nogo B activity in vitro and in vivo, and the inhibition of target cell growth in vitro and in vivo, which target cells harbor nucleic acids encoding Nogo B, and which methods comprise the administration of antisense or ribozymes targeting nucleic acids encoding Nogo B. In order to practice the invention over the scope claimed, it would require undue trial and error and undue experimentation beyond which is taught in the specification to practice the invention drawn to any route of administration of an antisense or ribozymes to an organism such that the target gene Nogo B is appropriately and specifically inhibited, and the growth of target cells which harbor Nogo B is also inhibited. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target gene such that Nogo B expression is inhibited *in vivo*, and further whereby target cell growth is inhibited *in vivo*. Since the specification fails to provide any particular guidance for the successful delivery

Art Unit: 1635

of antisense or ribozymes in any organisms, and since determination of these factors for a particular antisense or ribozyme in an organism is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 1-10, 27 and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by Bandman et al.

Bandman et al teach nucleic acid compositions comprising polynucleotides encoding amino acids from SEQ ID NO: 2, including from 10 to 50 contiguous nucleotides of SEQ ID NO: 1, which encode Nogo B, methods of making recombinant vectors and host cells comprising such polynucleotides, which methods also produce recombinant Nogo B. Bandman et al also teach compositions and methods for inhibiting the expression of SEQ ID NO: 2 (and hence inhibiting the activity of Nogo B), whereby target cell growth is inhibited in vitro, and which methods comprise administration of antisense or ribozymes targeting SEQ ID NO: 1 (See entire

Art Unit: 1635

text, especially abstract; column 2; column 18; column 27; SEQ ID NO: 2; and the alignment data attached to the reference).

Claim Rejections - 35 USC § 103.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 23-25, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bandman et al as applied to claims 1-10, 27 and 28 above, and further in view of Milner et al and James.

The claims are drawn to nucleic acids encoding and methods of expressing SEQ ID NO: 2, as well as being drawn to compositions and methods of cell growth inhibition in vitro, and

Art Unit: 1635

methods of inhibiting Nogo B activity in vitro comprising the administration of antisense or ribozymes targeting Nogo B, and which antisense comprise oligonucleotides comprising lengths between 8 and 50 nucleotides and comprising SEQ ID Nos: 3-6.

Bandman et al are relied upon as cited in the 102 rejection above.

Bandman et al do not teach the use of antisense oligonucleotides comprising SEQ ID Nos: 3-6.

Milner et al and James both teach methods of assessing the ability of antisense to inhibit expression of a target gene of known sequence, which antisense span the sequence of the known gene (See entire texts, especially 197-198 of James).

It would have been obvious to one of ordinary skill in the art to inhibit the expression of Nogo B using antisense oligonucleotides comprising 8-50 nucleotides in length, and comprising SEQ ID Nos: 3-6, because the nucleotide sequence of Nogo B was disclosed previously by Bandman et al, and Milner et al and James teach methods of assessing inhibition of a target gene of known sequence using antisense of various lengths, which antisense span the target gene. One of ordinary skill in the art would have been motivated to inhibit the expression of Nogo B, because it was disclosed by Bandman et al that proteins such as Nogo B are involved in various diseases and conditions such as neurogenitive diseases (See column 1 of Bandman et al). One of ordinary skill in the art would have expected that using such antisense as SEQ ID Nos: 3-6 cause inhibition of Nogo B expression, and inhibition of Nogo B expression provides insight into Nogo B's role in neurogenitive diseases or conditions.

Art Unit: 1635

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

February 12, 2001



ANDREW WANG
PATENT EXAMINER
TCL 600